ORAL LIQUID PHARMACEUTICAL COMPOSITIONS OF SERTRALINE

Field of the Invention

The present invention relates to oral liquid pharmaceutical compositions that include sertraline and pharmaceutically acceptable salts thereof. The invention also relates to processes for the preparation of the pharmaceutical compositions.

Background of the invention

Sertraline is a selective serotonin reuptake inhibitor (SSRI) indicated for the treatment of depression, obsessive-compulsive disorder, post-traumatic stress disorder and panic disorder. Chemically, sertraline is (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-nanphthalenamine and is sold under the brand name Zoloft® as tablets and capsules in the strengths of 25 mg, 50 mg and 100 mg.

Although the tablet and capsule dosage forms are a convenient mode of administering the required dose, in certain cases, such as in the case of children and elderly patients who have difficulty in swallowing, these dosage forms may not be the most preferable. With these dosage forms, patient compliance may be reduced and successful completion of long term therapy may not be possible. Therefore, a liquid dosage form of sertraline which is easy to take is desirable as this would be expected to improve overall patient compliance.

U.S. Patent No. 6,727,283 discloses an essentially non-aqueous liquid pharmaceutical concentrate composition of sertraline for oral administration. This patent describes essentially non-aqueous as being the amount of water that is present in the final drug product and further states that this amount is consistent with the amount of water potentially contributed by the active ingredient and/or by the excipients. The patent further points out that to be essentially non-aqueous according to the patent, no water is directly added to the final drug product. Finally, the patent states that about 10% is the upper limit of the amount of water that may be present in the oral concentrate. In this patent, sertraline or its salts are dissolved in a non-aqueous vehicle, such as alcohol and glycerine. However, the use of non-aqueous vehicles, and in particular alcohol, arguably should be minimized as it is unacceptable to some patients. In addition, the use of non-

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aqueous vehicles may not be economical and requires additional settings during manufacturing due to environmental considerations.

We have now surprisingly discovered that it is possible to prepare pharmaceutical compositions of sertraline having water at a proportion of the composition that is greater than 10% w/w. This improvement reduces the quantity of non-aqueous solvents necessary, which may be both environmentally friendly and economical. The oral liquid compositions have an acceptable taste and can be easily swallowed, thereby improving patient compliance.

Summary of the Invention

In one general aspect, there is provided a pharmaceutical composition that includes sertraline or a pharmaceutically acceptable salt thereof and water. The water is present at an amount that is greater than about 10% w/w to about 40% w/w of the composition.

Embodiments of the composition may include one or more of the following features. For example, the water may be present at an amount that is greater than about 10% w/w to about 25% w/w of the composition, greater than about 10% w/w to about 15% w/w of the composition, or between about 10.5% w/w and 12% w/w of the composition.

The pharmaceutically acceptable salt may be sertraline hydrochloride. The sertraline or pharmaceutically acceptable salt thereof may be present in an amount of about 0.1 mg/ml to about 70 mg/ml and, more particularly, about 15 mg/ml to about 30 mg/ml.

The composition may further include one or more non-aqueous vehicles, preservatives and flavouring agents. The non-aqueous vehicle may be one or more of ethanol, glycerine, propylene glycol or mixtures thereof. In particular, the non-aqueous vehicle may be a mixture of ethanol and glycerine.

The preservative may be one or more of butylated hydroxytoluene, butylated hydroxyanisole, propyl gallate, ascorbic acid, ascorbyl palmitate, sodium metabisulite, sodium bisulfite, sodium thiosulfate, sodium hydroxide, cystiene, ethylenediamine tetraacetic acid or its salts, citric acid, triethanolamine, thioglycerol, methyl paraben or propyl paraben. In particular, the preservative may be butylated hydroxytoluene.

The flavouring agent may be one or more of menthol, peppermint, spearmint, citrus, strawberry, raspberry, flavour blackcurrant, orange and grape fruit flavours, aspartame, saccharin sodium or mixtures thereof.

The composition may be in the form of an oral liquid concentrate. At least a portion of the water in the composition may be added and is not from the sertraline and/or excipients. The composition may be free of polyethylene glycol.

In another general aspect there is provided a process for the preparation of an orally administered liquid pharmaceutical composition. The process includes dissolving sertraline or a pharmaceutically acceptable salt thereof in one or more non-aqueous vehicles to form a solution; and adding water to the solution.

Embodiments of the process may include one or more of the following features or those described above. For example, the process may further include filtering the solution to which water has been added; and filling the filtered solution into a suitable container.

The water may be present at an amount that is greater than about 10% w/w to about 25% w/w of the composition. In particular, the amount may be greater than about 10% w/w to about 15% w/w of the composition and, even more particularly, the amount may be between about 10.5% w/w and 12% w/w of the composition.

The pharmaceutically acceptable salt may be sertraline hydrochloride. The sertraline or pharmaceutically acceptable salt thereof may be present in an amount of about 0.1 mg/ml to about 70 mg/ml and, more particularly, about 15 mg/ml to about 30 mg/ml.

The composition may further include one or more non-aqueous vehicles, preservatives and flavouring agents. The non-aqueous vehicle may be one or more of ethanol, glycerine, propylene glycol or mixtures thereof. In particular, the non-aqueous vehicle may be a mixture of ethanol and glycerine.

The process may still further include adding one or both of a preservative and a flavouring agent.

The preservative may be one or more of butylated hydroxytoluene, butylated hydroxyanisole, propyl gallate, ascorbic acid, ascorbyl palmitate, sodium metabisulite,

sodium bisulfite, sodium thiosulfate, sodium hydroxide, cystiene, ethylenediamine tetraacetic acid or its salts, citric acid, triethanolamine, thioglycerol, methyl paraben or propyl paraben. In particular, the preservative may be butylated hydroxytoluene.

The flavouring agent may be one or more of menthol, peppermint, spearmint, citrus, strawberry, raspberry, flavour blackcurrant, orange and grape fruit flavours, aspartame, saccharin sodium or mixtures thereof.

In another general aspect there is provided a method of treating one or more of depression, panic disorder, post-traumatic stress disorder, and obsessive compulsive disorder in a patient in need thereof. The method includes administering a pharmaceutical composition that includes sertraline or a pharmaceutically acceptable salt and water. The water is present in the composition at a concentration of greater than about 10% w/w to about 40% w/w of the composition.

Embodiments of the method may include one or more of the following features or those described above. For example, the method may further include diluting the pharmaceutical composition in an aqueous vehicle prior to dosing. The aqueous vehicle may be one or more of water, orange juice, ginger ale, lemon lime soda, lemonade, cranberry juice, grapefruit juice, tomato juice, pineapple juice or prune juice.

The details of one or more embodiments of the invention are set forth in the description below. Other features, objects and advantages of the invention will be apparent from the description and claims.

Detailed Description of the Invention

The inventors have now developed an oral liquid concentrate pharmaceutical composition containing sertraline or a pharmaceutically acceptable salt thereof. The oral liquid concentrate also includes between greater than about 10% w/w and about 40% w/w of water.

The term "oral liquid concentrate" as used herein refers to is a solution which includes sertraline or pharmaceutically acceptable salt thereof and which is diluted with an aqueous vehicle prior to dosing.

Sertraline or a pharmaceutically acceptable salt thereof includes sertraline free base and any other pharmaceutically acceptable salt that may be used to prepare the composition according to the invention. For example, hydrochloride or mesylate salts may be used. Sertraline may be present in the composition at an amount from about 0.1 mg/ml to about 70 mg/ml, particularly from about 15 mg/ml to about 30 mg/ml and more particularly at about 20 mg/ml.

Suitable water includes one or more of distilled water, purified water and deionised water. The water may be present in an amount of more than about 10% to about 40% w/w of the composition. Particularly, it can be up to about 25%, and more particularly, it can be up to about 15% w/w of the composition. For example, the water can be present at an amount that is between greater than about 10% and up to 11% or 12%, and amounts within that range.

Suitable non-aqueous vehicles include any non-toxic solvent which can solubilize sertraline and also is suitable for human consumption. For example, suitable non-aqueous vehicles include one or more of ethanol, glycerine and propylene glycol. The use of polyethylene glycol has been exemplified in U.S. Patent No. 6,727,283. However, we have found out that liquid PEGs are incompatible with sertraline hydrochloride and immediately result in discoloration when in physical contact and should be avoided. Particularly suitable vehicles are ethanol and glycerine. Ethanol may be present at a concentration of up to about 70%, particularly about 50%, and more particularly up to about 30% w/w of the composition. Suitable ethanols may be one or more of anhydrous ethanol or any suitable grade such as distilled ethanol or absolute ethanol. Glycerine may be present in an amount of up to about 90% w/w of the composition. Particularly, glycerin may be present in an amount up to about 80%, and more particularly up to about 75% w/w of the composition.

The oral liquid concentrate may include one or more preservatives and flavouring agents.

Suitable preservatives include one or more of antioxidants, metal chelators, metal complexing agents and antimicrobial agents or a combination thereof. For example, suitable preservatives include one or more of butylated hydroxytoluene, butylated hydroxyanisole, propyl gallate, ascorbic acid, ascorbyl palmitate, sodium metabisulite, sodium bisulfite, sodium thiosulfate, sodium hydroxide, cystiene, ethylenediamine

tetraacetic acid or its salts, citric acid, triethanolamine, thioglycerol, methyl paraben and propyl paraben. Particularly suitable is butylated hydroxytoluene. Preservatives may be present in an amount of about 0.01 to about 10 mg/ml, particularly from about 0.1 to about 5 mg/ml.

Suitable flavouring agents may include one or more of menthol, peppermint, spearmint, citrus, strawberry, raspberry, flavour blackcurrant, orange and grape fruit flavours. Sweeteners like aspartame and saccharin sodium can also be added as flavouring agents.

The oral concentrate as used herein is intended to be diluted prior to administration. The dilution can be done with a suitable aqueous vehicle including one or more of water, orange juice, ginger ale, lemon lime soda, lemonade, crane berry juice, grape fruit juice, tomato juice, pineapple juice and prune juice. The dilution may be done according to the dose required, i.e., the concentrate can be diluted with a sufficient quantity of the aqueous vehicle to provide a dose of sertraline, such as about 25 mg or 50 mg of sertraline.

The process of preparing the oral liquid concentrate involves simple manufacturing steps and conventional equipment. The process generally includes dissolving sertraline or a pharmaceutically acceptable salt thereof in a non-aqueous vehicle and adding water. Alternatively, the process may generally include dissolving sertraline in a mixture of non-aqueous vehicle and water and optionally adding flavouring agents and preservatives to the above solution. The solution is subsequently filtered and filled into suitable containers.

The oral liquid concentrate may be prepared by dissolving sertraline hydrochloride or a pharmaceutically acceptable salt thereof in a mixture of ethanol and a first portion of glycerine while stirring. The remaining portion of glycerine and water are added while stirring the above solution. The solution is then filtered and filled into a suitable container.

The oral liquid concentrate may also be prepared by dissolving sertraline hydrochloride or a pharmaceutically acceptable salt thereof in glycerine while stirring; adding water to the above solution with stirring; filtering; and filling the solution into a suitable container.

In yet another embodiment, the oral liquid concentrate is prepared by dissolving sertraline hydrochloride or a pharmaceutically acceptable salt thereof in propylene glycol while stirring; adding water to the above solution while stirring; filtering; and, filling the solution into a suitable container.

In still another embodiment, the oral liquid concentrate is prepared by dissolving sertraline hydrochloride or a pharmaceutically acceptable salt thereof in a mixture of ethanol and a first portion of propylene glycol while stirring; adding the remaining quantity or second portion of propylene glycol and water while stirring the above solution; filtering; and, filling the solution into a suitable container.

In another embodiment, the oral liquid concentrate is prepared by dissolving sertraline hydrochloride or a pharmaceutically acceptable salt thereof in propylene glycol while stirring; adding glycerine and water while stirring the above solution; filtering; and, filling the solution into a suitable container.

The following examples are intended to illustrate the invention and not to be construed as limiting the scope of the invention in any way. In particular, these examples show formulations with different amounts of water content added to the composition.

EXAMPLE 1 (17.7% water content)

Ingredient	**Quantity (mg/ml)**
Sertraline hydrochloride (eq. to 20 mg of sertraline)	22.36
Ethanol 99.9%	151
Menthol	0.5
Butylated hydroxytoluene	0.1
Glycerine	q.s.
Purified water	177.75
Total	**1000 ml**

Procedure

1. Butylated hydroxytoluene and menthol were dissolved in a first portion of ethanol under stirring.
2. Sertraline or a pharmaceutically acceptable salt thereof was dissolved in glycerine and the remaining quantity or second portion of ethanol, and this solution then was added to the solution of step (1) solution under stirring.
3. Purified water was added to the above solution of step (2) while stirring.

4. The final volume was made up with glycerine.
5. The above solution was filtered and packed into a suitable container.

EXAMPLE 2 (17.7% water content)

Ingredient	Quantity (mg/ml)
Sertraline hydrochloride (eq. to 20 mg of sertraline)	22.36
Menthol	0.5
Ethanol 99.9%	151
Butylated hydroxytoluene	0.1
Propylene glycol	q.s.
Purified water	177.75
Total	**1000ml**

Procedure

1. Menthol and butylated hydroxytoluene were dissolved in a first portion of ethanol under stirring.
2. Propylene glycol and the remaining quantity or second portion of ethanol were added to the solution of step (1) under stirring.
3. Sertraline or a pharmaceutically acceptable salt thereof was added to the above solution under stirring.
4. Purified water was added to the solution of step (3) under stirring.
5. The final volume was made up with propylene glycol.
6. The above solution was filtered and packed into a suitable container.

EXAMPLE 3 (17.7% water content)

Ingredient	Quantity (mg/ml)
Sertraline hydrochloride (eq. to 20 mg of sertraline)	22.36
Menthol	0.5
Butylated hydroxyanisole	0.1
Propylene glycol	q.s.
Purified water	177.75
Total	**1000 ml**

Procedure

1. Menthol and butylated hydroxyanisole were dissolved in a first portion of propylene glycol under stirring.
2. Sertraline or a pharmaceutically acceptable salt thereof was added to the solution of step (1) under stirring and purified water was added.
3. The final volume was made up with the second portion of propylene glycol.
4. The above solution was filtered and packed into a suitable container.

EXAMPLE 4 (12% water content)

Ingredient	Quantity (mg/ml)
Sertraline hydrochloride (eq. to 20 mg of sertraline)	22.56
Ethanol 99.9%	120
Menthol	0.125
Butylated hydroxytoluene	0.04
Glycerine	q.s.
Purified water	120
Total	**1000 ml**

Procedure

1. BHT and menthol were dissolved in ethanol under stirring.
2. The solution of step (1) was added to a portion of glycerine under stirring.
3. Sertraline was dissolved in the solution of step (2) under stirring.
4. Purified water was added to the solution of step (3) under stirring.
5. The final volume was made by adding glycerin.
6. The above solution was filtered and packed into a suitable container.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention. For example, based on the disclosure herein, it should be evident that the exemplary formulations provided above can be modified to include 10.5%, 11%, or 11.5% water by, for example, changing the amount of ethanol, glycerine, and/or propylene glycol in the composition.